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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,864	11/24/2000	David Scheinberg	D6126	4077

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,864	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7-22* is/are pending in the application.

4a) Of the above claim(s) *8-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 2 and 6.

Accordingly, claims 1, 3, 4-5, 7 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 1, 3, 4-5, 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

OK amended

Claims 1, 3-5, 7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct, at least once, comprising an alpha emitting isotope, and an antibody specific for said tumor, or fragment thereof, wherein the number of administrations of said construct necessary to kill said tumor increases as the size of said tumor increases.

The specification does not teach a method of killing a tumor greater than 1 mm in size, comprising administering a construct, "at least once", comprising an alpha emitting isotope, and an antibody specific for said tumor, or fragment thereof

The specification does not teach that the number of administrations of the claimed construct necessary to kill said tumor increases as the size of said tumor increases.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Rejection under 35 USC 112, first paragraph of claims 1, 3, 4-5, 7 pertaining to lack of enablement for a method for killing a solid tumor, using a construct comprising an antibody or an antibody fragment specific to said tumor, and an alpha emitting isotope remains for reasons already of record in paper No.6.

OK withdrawn

Applicant argues that claim 1 has been amended and thus rejection would be obviated.

Applicant's arguments set forth in paper No.9 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that a construct comprising an antibody and an alpha emitting isotope encompasses a composition comprising an antibody and an alpha emitting isotope that are put together and are not necessarily conjugated. Thus it is unpredictable that using the claimed construct, the alpha emitting isotope would be targeted to the tumor and that the claimed method would be effective in killing solid tumors.

Further, an antibody fragment could be a fragment which does not bind to the antigen. Thus it is unpredictable that using the claimed construct, the antibody fragment would be targeted to the tumor and that the claimed method would be effective in killing solid tumors.

2. Rejection under 35 USC 112, first paragraph of claim 7 pertaining to lack of enablement for a method for killing a solid tumor, comprising administering an effective dose of a construct comprising an antibody or an antibody fragment specific to said tumor, and an alpha emitting isotope, wherein said dose is from about 0.1 mg/m^2 to about 50 mg/m^2 remains for reasons already of record in paper No.6.

Applicant argues that as recited by the Examiner, to determine optimumn dosage is within the level of ordinary skill in the art. Applicant asserts that the dosage depends on the specific activity of the radionuclide and tumor to be treated, the size of the recipient, the ability of the recipient to tolerate a particular dosage and the tumor burden. Applicant further asserts that one would recognize that dosage of a radionuclide has a lethal limit, and as such one would not be motivated to try administering the maximun specific activity and dosage, i.e. 50,000 uCi, to a mouse.

Applicant's arguments set forth in paper No.9 have been considered but are not deemed to be persuasive for the following reasons:

The dose of 50mg/m^2 would seem to be one of ordinary skill in the art to be lethal and non-practical. Even with a dose of 50mg/m^2 and a relatively low level of specific activity, such as 2 mCi/mg, one still would expect an injection of 1000 uCi, which would be lethal according to Adams et al (of record, p.341, first column).

3. Rejection under 35 USC 112, first paragraph of claims 1, 3-5, 7 pertaining to lack of enablement for a method for killing a solid tumor of any size, remains for reasons already of record in paper No.6.

Applicant argues that the process in like peeling an onion, since bismuth 212 and 213 has short effective range, usually killing no more than 5 or 6 layers of cells. Applicant further asserts that the construct would be administered as many times as required to repeat the process of killing of 5-6 layers of tumor cells each time.

Applicant's arguments set forth in paper No.9 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the maximum volume of the disclosed treated tumors is 5mm x 5mm x 3.14/6 or about 13 mm^3.

It is unpredictable that repeated killing 5-6 layers of tumor cells each time, within the limit of toxicity of bismuth 212 and 213, would be adequate to reduce the size of large tumors, such as tumors of a volume of 936 mm^3 as taught by Hartman et al, which are 72 times as large as the treated tumors of the claimed invention. Due to severe toxicity including death by bismuth 212 and 213, it is not clear how many times one could administer the claimed labeled antibody in a week. Hartman et al (of record) teach that a large size tumor could at least double in size in every 8 days or even faster such as 50% more in size in every 2 days, with one treatment with B-212 labeled antibody (figure 6 on page 4367), and that large tumor having a volume of 936 mm^3 could not be treated with one injection of antibodies labeled with Bi-212, i.e. no reduction in the size of the tumor (p.4367, first column, first paragraph). Thus, since

from large tumors, the amount of tumor cells that are not killed would be overwhelmingly much larger than the outer 5 or 6 layers of cells, and since the tumor cells that are not killed would continue to multiply at a rate taught by Hartman et al, one could not predict that the size of the tumor would be reduced, because the number of tumor cells from new growth could mask or outnumber the number of cells from 5 or 6 outer layers of cells that are killed. Thus based on the teaching of Hartman et al, one could not predict that solid tumors having any size would be reduced in size or treated by repeated administration of the claimed Bi-213 labeled antibody.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claims 1, 3-5, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simonson et al, 1990, Cancer Res, 50 (3 Supp): 9855-9885, in view of Kasperson, FM et al, of record, and US PN=4,665,897.

Claims 1, 3-5, 7 are drawn to a method of killing a tumor greater than 1 mm in size, comprising administering a construct at least once, comprising an alpha emitting isotope, and an antibody specific for said tumor, or fragment thereof, wherein the number of administrations of said construct necessary to kill said tumor increases as the size of said tumor increases. Said alpha emitting isotope is bismuth-213, and has a specific activity from about 0.1 mCi/mg to about 50 mCi/mg, and is administered at a dose of about 0.1 mg/m^2 to about 50 mg/m^2. Said alpha emitting isotope is administered in a dose adequate to deliver a minimum of 1 alpha track per cell.

Simonson et al teach administration of 212-Bi labeled antibodies to mice previously injected with LS1744T cells which grow both as solid tumors and ascites in mice, wherein the mice develop ascites at about 20 days after injection of the tumor cells (p. 985s, second column, last paragraph), and only after the development of solid tumor (p. 987s, second column, first paragraph). Simonson et al teach that the specific activity of the labeled antibody is 5 to 10 uCi/ug (p.986s, first column, second paragraph), which is the same as 5 to 10 mCi/mg and is within the range of the claimed specific activity. Simonson et al further teach that for advanced tumors of 13 days after injection of tumor cells, with single and repeated administration of Bi-212 labeled antibody, 56% decrease in tumor mass is obtained (p.986s, first column, third paragraph and figure 1 on page 986s). Simonson et al teach that 13 days after injection, the tumor mass is 3 gm on average (figure 1).

Simonson et al do not teach a method of killing a tumor greater than 1 mm in size, comprising administering antibodies that are labeled with Bi-213, having at a dose of about 0.1 mg/m^2 to about 50 mg/m^2 or at a dose adequate to deliver a minimum of 1 alpha track per cell.

Kaspersen et al teach that Bi-213 can be an alternative to Bi-212, with the advantage of safer and easier production (p.475, first column, first paragraph).

PN=4,665,897 teach a method of treating tumors comprising administering antibodies containing inactive nuclide that could be rendered radioactive with externally generated radiation, wherein the steps of said method are repeated as many times as

necessary to effect remission or destruction of tumors (Claims 28, 35, 36). Said radiation includes alpha particles (claim 27).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to treat tumors of at least 1 mm in size using the method of Simonson et al, comprising administering an antibody labeled with Bi-212. Although Simonson et al do not teach that the treated tumors are at least 1 mm in size, one would have expected that the size of the solid tumors taught by Simonson et al would be at least 1 mm in size, because the solid tumors taught by Simonson et al have 3gm average in weight, and are advanced tumors after 13 days of growth. It would have been obvious to substitute Bi-212 with Bi-213, because Bi-213 has the advantage of safer and easier production, as taught by Kasperson et al. It would have been obvious to administer the labeled antibody at least once or repeatly, as taught by Simonson et al, and PN=4,665,897, wherein the number of administrations of the labeled antibody necessary to kill said tumor increases as the size of said tumor increases, to ensure destruction of the tumors. With regards to the dosage of the labeled antibodies recited in claims 5, 7, to determine optimum dosage is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425. One of ordinary skill in the art would have been motivated to treat tumors having at least 1mm in size using antibodies labeled with Bi-213 with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

November 15, 2002

ANTHONY C. CAPUTA
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